From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 November 1998 (13.11.98)	
International application No. PCT/CA98/00274	**Applicant's or agent's file reference** 9577-4 LAB
International filing date (day/month/year) 03 April 1998 (03.04.98)	**Priority date** (day/month/year) 21 April 1997 (21.04.97)
Applicant ODIDI, Isa et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

22 October 1998 (22.10.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Nicola Wolff
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

2337644

From the INTERNATIONAL BUREAU

PCT

To:
RO: CA

COMMUNICATION IN CASES FOR WHICH NO OTHER FORM IS APPLICABLE

Date of mailing (*day/month/year*) 31 August 1998 (31.08.1998)	
Applicant's or agent's file reference 9577-4 LAB	**REPLY DUE** see paragraph 1 below
International application No. PCT/CA98/00274	International filing date (*day/month/year*) 03 April 1998 (03.04.1998)
Applicant ODIDI, Isa	

1. ☐ REPLY DUE within _____ months/days from the above date of mailing

☐ NO REPLY DUE, however, see below

☒ IMPORTANT COMMUNICATION

☐ INFORMATION ONLY

2. COMMUNICATION:

NOTIFICATION OF (CANCELLATION)(CORRECTION) OF PRIORITY CLAIM

The applicant is hereby notified that the International Bureau has taken the following action in respect of the priority claim(s) made in the above-identified PCT international application.

The priority claim(s), identified below, has(have), in accordance with the applicant's request been (corrected to read/cancelled):

(US) (21 April 1997 (21.04.97)) (60/036,551).

A copy of this notification has been sent to the receiving Office, the International Searching Authority, and the designated Offices (*which have already been notified of the receipt of the record copy*).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
S. Cruz

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BARTOSZEWICZ, L.
Sim & McBurney
330 University Avenue
6th floor
Toronto, Ontario M5G 1R7
CANADA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.07.99
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
9577-4 LAB	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00274	03/04/1998	21/04/1997

Applicant
ODIDI, Isa et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9577-4 LAB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00274	03/04/1998	21/04/1997
International Patent Classification (IPC) or national classification and IPC A61K9/22		
Applicant ODIDI, Isa et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/10/1998	16.07.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Ortega Plaza, M.D. Telephone No. (+49-89) 2399 8284

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00274

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-17	as originally filed				

Claims, No.:

1-10,23 (part), 24-29	as originally filed				
11-22,23 (part)	as received on	11/05/1999	with letter of	11/05/1999	

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 27.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does

not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 27 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☒ the claims, or said claims Nos. 27 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-9, 15, 19-26
	No:	Claims	1-6, 10, 12-14, 16-18, 28, 29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26, 28,29
Industrial applicability (IA)	Yes:	Claims	1-26, 28, 29
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III.

1. The composition as claimed in claim 27 relates to a "tablet which demonstrates the following cumulative percent release dissolution criteria using a pH gradient method of dissolution; 0-40% released in 1 hour in dissolution media of pH 1.50, 0-50% released in 2 hours in dissolution media of pH 4.5, 5-70% released in 2 hours in dissolution media of pH 6.5, 20-100% released in 15 hours in dissolution media of pH 7.5."

   No information with respect to the methodology implied above could be found in the description. Moreover, no support could be found in the description as originally filed for the data appearing in said claim 27.

Section V.

1. The following documents have been considered for the establishment of the present preliminary report:

   D1 = US-A-5000962
   D2 = EP-A-0226884
   D3 = Derwent abstract of JP-A-03206039
   D4 = EP-A-0253490
   D5 = EP-A-0157695
   D6 = US-A-5015479
   D7 = US-A-5451409
   D8 = EP-A-0468436
   D9 = Shan-Yang Lin, European Journal of pharmaceutics and Biopharmaceutics, 42(3), 193-198 (1996).
   D10 = US-A-4601894 (cited in the description)

2. Claim 1 relates to a controlled release pharmaceutical composition comprising:

   a) at least one pharmaceutically active substance
   b) a first "intelligent" polymer component

c) a second "intelligent" polymer component having **opposite wettability** characteristics to said first "intelligent" polymer component

the first and the second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight.

D1 discloses controlled release pharmaceutical composition comprising as pharmaceutically active substance diltiazem and further comprising hydroxymethyl cellulose or hydroxyethylcellulose used alone or in combination (cf. column 2, lines 58-61). Moreover, the compositions disclosed in D1 further comprise ethylcellulose as hydrophobic component (cf. column 4 and examples 2 and 3). Therefore, the presently claimed subject-matter (cf. claims 1-5, 6, 14, 16, 28) lacks novelty over the contents of D1. The feature "not less than **about** 5% by weight ethylcellulose" does not exclude the content 4% by wt. ethylcellulose (cf. D1). The said claims do not include the technical feature that the pharmaceutically active ingredient is incorporated within a **homogeneous matrix** comprising the two polymers having opposing wettability. Accordingly, in the absence of the said feature the mentioned claims encompass the tabletts disclosed in D1.

D2 discloses controlled release pharmaceutical compositions as those claimed in claims 1,2,5,10, 16-18, 28 and 29 (cf. i.a. example 1, the composition comprising diltiazem, hydroxypropylmethylcellulose and ethylcellulose and pages 10 to 12). D2 also discloses compositions further comprising coating agents and additives as those defined in the above mentioned claims 5,10, 17,18.

The pharmaceutical compositions disclosed in D3 fall within the scope of present claim 1 (2,3,5,10,12,13,16,29) since they comprise nifedipine as pharmaceutically active substance and further comprise ethylcellulose (EC) and hydroxypropylmethylcellulose.

D4 discloses controlled release pharmaceutical compositions comprising carbidopa/levodopa as pharmaceutically active substance and further comprising a system of two polymers with opposed hydrophilicity/hydrophobicity

characteristics. The polymer components hydroxypropylmethylcellulose and ethylcellulose (EC) and are listed on page 3. Moreover, since claim 1 does not include specific definitions of the polymer components the composition of example 3 of D4 falls within its scope. Additionally, the pharmaceutically active substance(s) are dispersed within a polymer matrix in the compositions of D4.

The contents of D5 are novelty destroying for the subject-matter claimed in claims 1- and 8 since it discloses controlled release pharmaceutical compositions comprising a pharmaceutically active substance (cf. page 12), ethyl cellulose and hydroxypropylmethylcellulose. The compositions of D5 further comprise a surface active agent (cf. i.a. examples 3-4 of D5 and compare with present claim 8).

The present compositions appear to be novel over the compositions disclosed in D6, D7, D9 basically, in view that they are comprising two different polymer components having opposite wettability characteristics.

The sustained release compositions disclosed in D8 fall within the scope of present claim 1 since they are comprising a pharmaceutically active substance (theophylline), ethyl cellulose and hydroxypropylcellulose. The method for preparing the compostions of D8 differs from the presently claimed method (cf. claim 23) basically due to the fact that the pharmaceutically active substance is worked out separatedly with each polymer component to form a two seprate sustained release powders which are then mixed together (cf. example 7 of D8). The compositions as defined in claim 1 lack novelty since there is not indication to the homogeneous polymer matrix.

The subject-matter claimed in claim 1 lacks novelty vis-à-vis the contents of D10 in view of the fact that D10 discloses controlled release pharmaceutical compositions comprising at least one pharmaceutically active substance (they comprise three) within a uniform matrix comprising as carrier hydroxypropylcellulose and ethyl cellulose.

It is to be stressed that the statement of a different mechanism for achieving the purpose of controlled release cannot serve to establish novelty over the prior art compositions as far as such effect is not linked to **new technical features**

included in the claims for defining the subject-matter for which protection is sought. The broadly and vaguely formulated claims have the effect that they encompass known compositions and hence the **claimed** subject-matter lacks novelty. Moreover, contrary to Applicant's comments claim 1 does not exclude the option of having only one first intelligent polymer and one second intelligent polymer. Nothing in claim 1 presupposes that the hydrophilic component comprises **two** polymers and the hydrophobic component comprises **one** polymer.

3. The problem underlying the present patent application appears to lie in the provision of further controlled release pharmaceutical compositions useful for sustained release delivery of pharmaceutically active substances.
It becomes evident from the analysis of the prior art made in point 2 above that the presently claimed subject-matter encompasses known solutions for the said technical problem. Moreover, those claims which appear to be novel in the light of the prior art cited above, merely differ therefrom in the choice and/or combination of known pharmaceutically acceptable additives. Accordingly, in the absence of any proven unexpected effect over the closest known controlled release pharmaceutical compositions, the presently claimed subject-matter lacks an inventive step.

Section VIII.

1. Claims 1, 14 and 19 do not meet the requirements of Article 6 PCT for the following reasons.

The mentioned claims do not include all the technical features which should characterize the invention in a clear and complete manner as contribution to the art. The mentioned claims are silent about the fact that the pharmaceutically active ingredient is incorporated within a **homogeneous matrix** comprising the two polymers having opposing wettability (cf. pages 4, line 36 and 8, line 24). Other essential features are the proportion of each polymers in the polymer blend, the hydrophobicity and hydrophilicity of the polymers (cf. page 5).

Moreover, the use of broad and vague expressions such as "intelligent polymer" renders obscure the scope for which protection has been sought (cf. claim 1). Moreover, such an expression has no standard meaning in the polymer field and has not been defined in the description.

Additionally, the expression "the polymer components being effective for controlled release of said pharmaceutically active substance from said composition" relates to the result-to-be-achieved and is insufficient for defining the nature of the polymer components.

The fact that the amount of ethylcellulose in the composition **should not be less than 5% wt/wt** is lacking in claim 1. This is an essential feature of the invention (cf. i.a. page 8).

The use of the expression "about" in connexion with ranges of values of essential parameters renders obscure the scope for which protection is sought (cf. for instance "about" in claim 14).

The technical feature "having a water contact angle ...." does not bring any actual restriction with respect to the nature of the pharmaceutically active substance, in view of the broad range values for the cosine function. This is proven by the list of possible agents given on pages 10-12 of the description.

11. The composition of claim 10, wherein said channeling agent is anhydrous lactose.

12. The composition of claim 1, wherein said composition further comprises 5% to 30% compression enhancer.

13. The composition of claim 10, wherein said compression enhancer is microcrystalline cellulose.

14. A controlled release pharmaceutical composition comprising:

(a) from about 0.5% to about 70% by weight of a pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) not less than about 5% by weight ethylcellulose;

(c) about 1:100 to 100:1 hydroxycellulose and hydroxypropyl methyl cellulose by weight;

(d) about 0.25% to 5% excipients; and

(e) about 0.5% to 15% surface active agents.

15. The composition of claim 14, wherein said composition additionally comprises

- about 10% to 70% channeling agents; and
- about 5% to 30% compression enhancers.

16. The composition as claimed in any one of claims 1 to 15, made in the form of a compressed tablet.

17. The tableted composition of claim 16, wherein said tableted composition has a anionic copolymer coating.

18. The tableted composition of claim 17, wherein said copolymer coating comprises methacrylic acid and methyl methacrylate, from about 0% to 25% plasticizer, from about 0% to 25% pigment, from about 0% to 30% glidant and from about 0% to 30% lubricant.

19. A controlled release composition, the composition comprising a therapeutically effective amount of a pharmaceutically active ingredient having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848; two groups of intelligent polymers having opposing wettability characteristics, one group demonstrating a stronger tendency towards hydrophobicity and present in an amount not less than 5% wt/wt and the other group having a

stronger tendency towards hydrophilicity and present in the ratio of about 1:100 and 100:1 by weight, the polymers being ethylcellulose (EC) as a more strongly hydrophobic and hydroxyethylcellulose (HEC) and hydroxypropyl methylcellulose (HPMC) as more strongly hydrophilic, about 0.25% to 5% silicon dioxide; and about 0.5% to 15% sodium lauryl sulfate.

20. The composition of claim 19, wherein said composition additionally comprises about 10% to 70% anhydrous lactose and about 5% to 30% microcrystalline cellulose.

21. The composition of claim 18 or 20, wherein said composition is provided as a tablet and has a coating composition comprising anionic copolymers sufficient to obtain about 0.5 to 15 mg per cm^2 of tablet.

22. The composition of claim 21, wherein said coating composition additionally comprises from about 0 to 25% plasticizer, about 0 to 25% pigment, about 0 to 30% and about 0 to 30% lubricant.

23. A process for the manufacture of a sustained release composition of pharmaceutically active substance, said process comprising:

(a) admixing a pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848:

(b) blending the pharmaceutically active ingredient with about 5 to 25% hydroxypropyl methylcellulose, about 1 to 25% hydroxyethylcellulose, about 0.25% to 5% suitable pharmaceutical excipients, about 0.5% to 15% suitable surface active agents, and about 10% to 70% chanelling agents in a high shear mixer until a homogeneous mixture is obtained;

(c) granulating the homogeneous blend with isopropyl alcohol (99%) in a planetary or high shear mixer;

(d) drying the wet granules to a loss on drying of about <3% and organic volatile impurities of isopropyl alcohol about <15000 ppm;

(e) milling the dry granules to about <1500 microns;

(f) adding and blending about 5% to 70% of ethylcellulose having 30-60% ethoxyl content and a vicosity of 60- 100 cps to the dry milled granules until a homogeneous blend is obtained;

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BARTOSZEWICZ, L.
Sim & McBurney
330 University Avenue
6th floor
Toronto, Ontario M5G 1R7
CANADA

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	11. 02. 99
Applicant's or agent's file reference: 9577-4 LAB	**REPLY DUE** within ~~3~~ 2 **month(s)** from the above date of mailing

International application no.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00274	03/04/1998	21/04/1997

International Patent Classification (IPC) or both national classification and IPC
A61K9/22

Applicant
ODIDI, Isa et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This report contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and / or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 21/08/1999

Name and mailing address of the international preliminary examining authority
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer / Examiner
Ortega Plaza, M.D.

Formalities officer (incl. extension of time limits)
Bleeker, M
Telephone No. (+49-89) 2399-8141

CH

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-17 as originally filed

Claims, No.:

1-29 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 27,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 27 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☒ the claims, or said claims Nos. 27 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6, 10, 12-14, 16-18, 28, 29
Inventive step (IS)	Claims	1-26, 28,29
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III.

1. The composition as claimed in claim 27 relates to a "tablet which demonstrates the following cumulative percent release dissolution criteria using a pH gradient method of dissolution; 0-40% released in 1 hour in dissolution media of pH 1.50, 0-50% released in 2 hours in dissolution media of pH 4.5, 5-70% released in 2 hours in dissolution media of pH 6.5, 20-100% released in 15 hours in dissolution media of pH 7.5."

   No information with respect to the methodology implied above could be found in the description. Moreover, no support could be found in the description as originally filed for the data appearing in said claim 27.

Section V.

1. The following documents have been considered for the establishment of the present written opinion:

   D1 = US-A-5000962
   D2 = EP-A-0226884
   D3 = Derwent abstract of JP-A-03206039
   D4 = EP-A-0253490
   D5 = EP-A-0157695
   D6 = US-A-5015479
   D7 = US-A-5451409
   D8 = EP-A-0468436
   D9 = Shan-Yang Lin, European Journal of pharmaceutics and Biopharmaceutics, 42(3), 193-198 (1996).
   D10 = US-A-4601894 (cited in the description)

2. Claim 1 relates to a controlled release pharmaceutical composition comprising:

   a) at least one pharmaceutically active substance
   b) a first "intelligent" polymer component

c) a second "intelligent" polymer component having **opposite wettability** characteristics to said first "intelligent" polymer component

the first and the second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight.

D1 discloses controlled release pharmaceutical composition comprising as pharmaceutically active substance diltiazem and further comprising hydroxymethyl cellulose or hydroxyethylcellulose used alone or in combination (cf. column 2, lines 58-61). Moreover, the compositions disclosed in D1 further comprise ethylcellulose as hydrophobic component (cf. column 4 and examples 2 and 3). Therefore, the presently claimed subject-matter (cf. claims 1-5, 6, 14, 16, 28) lacks novelty over the contents of D1. The said claims do not include the technical feature that the pharmaceutically active ingredient is incorporated within a **homogeneous matrix** comprising the two polymers having opposing wettability. Accordingly, in the absence of the said feature the mentioned claims encompass the tabletts disclosed in D1.

D2 discloses controlled release pharmaceutical compositions as those claimed in claims 1,2,5,10, 16-18, 28 and 29 (cf. i.a. example 1, the composition comprising diltiazem, hydroxypropylmethylcellulose and ethylcellulose and pages 10 to 12). D2 also discloses compositions further comprising coating agents and additives as those defined in the above mentioned claims 5,10, 17,18.

The pharmaceutical compositions disclosed in D3 fall within the scope of present claim 1 (2,3,5,10,12,13,16,29) since they comprise nifedipine as pharmaceutically active substance and further comprise ethylcellulose (EC) and hydroxypropylmethylcellulose.

D4 discloses controlled release pharmaceutical compositions comprising carbidopa/levodopa as pharmaceutically active substance and further comprising a system of two polymers with opposed hydrophilicity/hydrophobicity characteristics. The polymer components hydroxypropylmethylcellulose and ethylcellulose (EC) and are listed on page 3. Moreover, since claim 1 does not

include specific definitions of the polymer components the composition of example 3 of D4 falls within its scope. Additionally, the pharmaceutically active substance(s) are dispersed within a polymer matrix in the compositions of D4.

The contents of D5 are novelty destroying for the subject-matter claimed in claims 1- and 8 since it discloses controlled release pharmaceutical compositions comprising a pharmaceutically active substance (cf. page 12), ethyl cellulose and hydroxypropylmethylcellulose. The compositions of D5 further comprise a surface active agent (cf. i.a. examples 3-4 of D5 and compare with present claim 8).

The present compositions appear to be novel over the compositions disclosed in D6, D7, D9 basically, in view that they are comprising two different polymer components having opposite wettability characteristics.

The sustained release compositions disclosed in D8 fall within the scope of present claim 1 since they are comprising a pharmaceutically active substance (theophylline), ethyl cellulose and hydroxypropylcellulose. The method for preparing the compostions of D8 differs from the presently claimed method (cf. claim 23) basically due to the fact that the pharmaceutically active substance is worked out separatedly with each polymer component to form a two seprate sustained release powders which are then mixed together (cf. example 7 of D8). The compositions as defined in claim 1 lack novelty since there is not indication to the homogeneous polymer matrix.

The subject-matter claimed in claim 1 lacks novelty vis-à-vis the contents of D10 in view of the fact that D10 discloses controlled release pharmaceutical compositions comprising at least one pharmaceutically active substance (they comprise three) within a uniform matrix comprising as carrier hydroxypropylcellulose and ethyl cellulose.

3. The problem underlying the present patent application appears to lie in the provision of further controlled release pharmaceutical compositions useful for sustained release delivery of pharmaceutically active substances.
It becomes evident from the analysis of the prior art made in point 2 above that

the presently claimed subject-matter relates to a known solution for the said technical problem. Moreover, those claims which appear to be novel in the light of the prior art cited above, merely differ therefrom in the choice and/or combination of known pharmaceutically acceptable additives. Accordingly, in the absence of any proven unexpected effect over the closest known controlled release pharmaceutical compositions, the presently claimed subject-matter lacks an inventive step.

Section VIII.

1. Claims 1, 14 and 19 do not meet the requirements of Article 6 PCT for the following reasons.

   The mentioned claims do not include all the technical features which should characterize the invention in a clear and complete manner as contribution to the art. The mentioned claims are silent about the fact that the pharmaceutically active ingredient is incorporated within a **homogeneous matrix** comprising the two polymers having opposing wettability (cf. pages 4, line 36 and 8, line 24). Other essential features are the proportion of each polymers in the polymer blend, the hydrophobicity and hydrophilicity of the polymers (cf. page 5).

   Moreover, the use of broad and vague expressions such as "intelligent polymer" renders obscure the scope for which protection has been sought (cf. claim 1). Moreover, such an expression has no standard meaning in the polymer field and has not been defined in the description.

   Additionally, the expression "the polymer components being effective for controlled release of said pharmaceutically active substance from said composition" relates to the result-to-be-achieved and is insufficient for defining the nature of the polymer components.

   The fact that the amount of **ethylcellulose** in the composition **should not be less than 5% wt/wt** is lacking in claim 1. This is an essential feature of the invention (cf. i.a. page 8).

In claims 14 and 19 the ratio of one polymer component to the other is stated to be 1:100 to 100:1, however, it is lacking that it is **by weight**.

The use of the expression "about" in connexion with ranges of values of essential parameters renders obscure the scope for which protection is sought (cf. for instance "about" in claim 14).

The technical feature "having a water contact angle ...." does not bring any actual restriction with respect to the nature of the pharmaceutically active substance, in view of the broad range values for the *cosine* function. This is proven by the list of possible agents given on pages 10-12 of the description.

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Correspondence with the EPO on PCT Chapter II demands

In order to ensure that your PCT Chapter II demand is dealt with as promptly as possible you are requested to use the enclosed self-adhesive labels with any correspondence relating to the demand sent to the Munich Office.

One of these labels should be affixed to a prominent place in the upper part of the letter or form etc. which you are filing.

PATENT COOPERATION TREATY

PCT

09/403437

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
9577-4 LAB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 98/ 00274	03/04/1998	05/04/1997
Applicant		
ODIDI, Isa et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

   CONTROLLED RELEASE FORMULATIONS USING INTELLIGENT POLYMERS

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 98/00274

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/22

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 000 962 A (SANGEKAR ET AL.) 19 March 1991 see column 6; example 3 ---	1,2,5, 10,11, 16,27,28
X	EP 0 226 884 A (COLOMBO ET AL.) 1 July 1987 see page 10 - page 12; example 1 ---	1,2,5, 10, 16-18,29
X	DATABASE WPI Week 9142 Derwent Publications Ltd., London, GB; AN 91-307312 XP002079685 & JP 03 206039 A (KYOTO PHARM IND CO LTD) , 9 September 1991 see abstract --- -/--	1-3,5, 10,12, 13,16,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
6 October 1998	15/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 98/00274

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 253 490 A (MERCK & CO) 20 January 1988 see page 8; example 3 see claims 1-3,5-7	1-3
X	EP 0 157 695 A (FOREST LABORATORIES, INC.) 9 October 1985 see page 19 - page 20; examples 3,4	1-3,8
Y	US 5 015 479 A (MULLIGAN ET AL.) 14 May 1991 see column 6; example 10	4
Y	US 5 451 409 A (RENCHER ET AL.) 19 September 1995 see claim 1	4
A	EP 0 468 436 A (SS PHARMACEUTICAL CO., LTD.) 29 January 1992 see page 12; example 7	23
A	SHAN-YANG LIN ET AL.: "water uptake and drug release behaviour of drug-loaded compacts prepared from different grades of ethylcellulose" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 42, no. 3, June 1996, pages 193-198, XP000589998 Amsterdam (NL) see the whole document	23

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 98/00274

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5000962 A	19-03-1991	NONE	
EP 226884 A	01-07-1987	AU 594992 B	22-03-1990
		AU 6672586 A	25-06-1987
		CA 1298479 A	07-04-1992
		JP 2535339 B	18-09-1996
		JP 62155211 A	10-07-1987
		US 4839177 A	13-06-1989
EP 253490 A	20-01-1988	AU 597670 B	07-06-1990
		AU 7422887 A	17-12-1987
		CY 1578 A	20-12-1991
		DK 170514 B	09-10-1995
		HK 56191 A	26-07-1991
		IE 60508 B	27-07-1994
		JP 1715235 C	27-11-1992
		JP 4000045 B	06-01-1992
		JP 63054319 A	08-03-1988
		KR 9502882 B	28-03-1995
		PT 85049 B	08-03-1990
		US 4900755 A	13-02-1990
		US 4983400 A	08-01-1991
		ZA 8704233 A	14-12-1987
EP 157695 A	09-10-1985	US 4795327 A	03-01-1989
		CA 1240925 A	23-08-1988
		DE 3583694 A	12-09-1991
		DK 136385 A,B,	27-09-1985
		JP 60218329 A	01-11-1985
		US 4849229 A	18-07-1989
US 5015479 A	14-05-1991	NONE	
US 5451409 A	19-09-1995	NONE	
EP 468436 A	29-01-1992	JP 2572673 B	16-01-1997
		JP 4082825 A	16-03-1992
		CA 2046845 A	26-01-1992
		DE 69128569 D	12-02-1998
		DE 69128569 T	16-04-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 98/00274

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 468436 A		ES 2111547 T	16-03-1998
		US 5164193 A	17-11-1992

09/403437

REC'D 20 JUL 1999
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9577-4 LAB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00274	03/04/1998	21/04/1997
International Patent Classification (IPC) or national classification and IPC A61K9/22		
Applicant ODIDI, Isa et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/10/1998	7.6.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Ortega Plaza, M.D. Telephone No. (+49-89) 2399 8284

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00274

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-17	as originally filed				

Claims, No.:

1-10,23 (part), 24-29	as originally filed				
11-22,23 (part)	as received on	11/05/1999	with letter of	11/05/1999	

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 27.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does

not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 27 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☒ the claims, or said claims Nos. 27 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-9, 15, 19-26
	No:	Claims	1-6, 10, 12-14, 16-18, 28, 29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26, 28,29
Industrial applicability (IA)	Yes:	Claims	1-26, 28, 29
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III.

1. The composition as claimed in claim 27 relates to a "tablet which demonstrates the following cumulative percent release dissolution criteria using a pH gradient method of dissolution; 0-40% released in 1 hour in dissolution media of pH 1.50, 0-50% released in 2 hours in dissolution media of pH 4.5, 5-70% released in 2 hours in dissolution media of pH 6.5, 20-100% released in 15 hours in dissolution media of pH 7.5."

   No information with respect to the methodology implied above could be found in the description. Moreover, no support could be found in the description as originally filed for the data appearing in said claim 27.

Section V.

1. The following documents have been considered for the establishment of the present preliminary report:

   D1 = US-A-5000962
   D2 = EP-A-0226884
   D3 = Derwent abstract of JP-A-03206039
   D4 = EP-A-0253490
   D5 = EP-A-0157695
   D6 = US-A-5015479
   D7 = US-A-5451409
   D8 = EP-A-0468436
   D9 = Shan-Yang Lin, European Journal of pharmaceutics and Biopharmaceutics, 42(3), 193-198 (1996).
   D10 = US-A-4601894 (cited in the description)

2. Claim 1 relates to a controlled release pharmaceutical composition comprising:

   a) at least one pharmaceutically active substance
   b) a first "intelligent" polymer component

c) a second "intelligent" polymer component having **opposite wettability** characteristics to said first "intelligent" polymer component

the first and the second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight.

D1 discloses controlled release pharmaceutical composition comprising as pharmaceutically active substance diltiazem and further comprising hydroxymethyl cellulose or hydroxyethylcellulose used alone or in combination (cf. column 2, lines 58-61). Moreover, the compositions disclosed in D1 further comprise ethylcellulose as hydrophobic component (cf. column 4 and examples 2 and 3). Therefore, the presently claimed subject-matter (cf. claims 1-5, 6, 14, 16, 28) lacks novelty over the contents of D1. The feature "not less than **about** 5% by weight ethylcellulose" does not exclude the content 4% by wt. ethylcellulose (cf. D1). The said claims do not include the technical feature that the pharmaceutically active ingredient is incorporated within a **homogeneous matrix** comprising the two polymers having opposing wettability. Accordingly, in the absence of the said feature the mentioned claims encompass the tabletts disclosed in D1.

D2 discloses controlled release pharmaceutical compositions as those claimed in claims 1,2,5,10, 16-18, 28 and 29 (cf. i.a. example 1, the composition comprising diltiazem, hydroxypropylmethylcellulose and ethylcellulose and pages 10 to 12). D2 also discloses compositions further comprising coating agents and additives as those defined in the above mentioned claims 5,10, 17,18.

The pharmaceutical compositions disclosed in D3 fall within the scope of present claim 1 (2,3,5,10,12,13,16,29) since they comprise nifedipine as pharmaceutically active substance and further comprise ethylcellulose (EC) and hydroxypropylmethylcellulose.

D4 discloses controlled release pharmaceutical compositions comprising carbidopa/levodopa as pharmaceutically active substance and further comprising a system of two polymers with opposed hydrophilicity/hydrophobicity

characteristics. The polymer components hydroxypropylmethylcellulose and ethylcellulose (EC) and are listed on page 3. Moreover, since claim 1 does not include specific definitions of the polymer components the composition of example 3 of D4 falls within its scope. Additionally, the pharmaceutically active substance(s) are dispersed within a polymer matrix in the compositions of D4.

The contents of D5 are novelty destroying for the subject-matter claimed in claims 1- and 8 since it discloses controlled release pharmaceutical compositions comprising a pharmaceutically active substance (cf. page 12), ethyl cellulose and hydroxypropylmethylcellulose. The compositions of D5 further comprise a surface active agent (cf. i.a. examples 3-4 of D5 and compare with present claim 8).

The present compositions appear to be novel over the compositions disclosed in D6, D7, D9 basically, in view that they are comprising two different polymer components having opposite wettability characteristics.

The sustained release compositions disclosed in D8 fall within the scope of present claim 1 since they are comprising a pharmaceutically active substance (theophylline), ethyl cellulose and hydroxypropylcellulose. The method for preparing the compostions of D8 differs from the presently claimed method (cf. claim 23) basically due to the fact that the pharmaceutically active substance is worked out separatedly with each polymer component to form a two seprate sustained release powders which are then mixed together (cf. example 7 of D8). The compositions as defined in claim 1 lack novelty since there is not indication to the homogeneous polymer matrix.

The subject-matter claimed in claim 1 lacks novelty vis-à-vis the contents of D10 in view of the fact that D10 discloses controlled release pharmaceutical compositions comprising at least one pharmaceutically active substance (they comprise three) within a uniform matrix comprising as carrier hydroxypropylcellulose and ethyl cellulose.

It is to be stressed that the statement of a different mechanism for achieving the purpose of controlled release cannot serve to establish novelty over the prior art compositions as far as such effect is not linked to **new technical features**

included in the claims for defining the subject-matter for which protection is sought. The broadly and vaguely formulated claims have the effect that they encompass known compositions and hence the **claimed** subject-matter lacks novelty. Moreover, contrary to Applicant's comments claim 1 does not exclude the option of having only one first intelligent polymer and one second intelligent polymer. Nothing in claim 1 presupposes that the hydrophilic component comprises **two** polymers and the hydrophobic component comprises **one** polymer.

3. The problem underlying the present patent application appears to lie in the provision of further controlled release pharmaceutical compositions useful for sustained release delivery of pharmaceutically active substances.
It becomes evident from the analysis of the prior art made in point 2 above that the presently claimed subject-matter encompasses known solutions for the said technical problem. Moreover, those claims which appear to be novel in the light of the prior art cited above, merely differ therefrom in the choice and/or combination of known pharmaceutically acceptable additives. Accordingly, in the absence of any proven unexpected effect over the closest known controlled release pharmaceutical compositions, the presently claimed subject-matter lacks an inventive step.

Section VIII.

1. Claims 1, 14 and 19 do not meet the requirements of Article 6 PCT for the following reasons.

   The mentioned claims do not include all the technical features which should characterize the invention in a clear and complete manner as contribution to the art. The mentioned claims are silent about the fact that the pharmaceutically active ingredient is incorporated within a **homogeneous matrix** comprising the two polymers having opposing wettability (cf. pages 4, line 36 and 8, line 24). Other essential features are the proportion of each polymers in the polymer blend, the hydrophobicity and hydrophilicity of the polymers (cf. page 5).

Moreover, the use of broad and vague expressions such as "intelligent polymer" renders obscure the scope for which protection has been sought (cf. claim 1). Moreover, such an expression has no standard meaning in the polymer field and has not been defined in the description.

Additionally, the expression "the polymer components being effective for controlled release of said pharmaceutically active substance from said composition" relates to the result-to-be-achieved and is insufficient for defining the nature of the polymer components.

The fact that the amount of ethylcellulose in the composition **should not be less than 5% wt/wt** is lacking in claim 1. This is an essential feature of the invention (cf. i.a. page 8).

The use of the expression "about" in connexion with ranges of values of essential parameters renders obscure the scope for which protection is sought (cf. for instance "about" in claim 14).

The technical feature "having a water contact angle ...." does not bring any actual restriction with respect to the nature of the pharmaceutically active substance, in view of the broad range values for the cosine function. This is proven by the list of possible agents given on pages 10-12 of the description.

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Writer's Ext. **283**

Serial No.: PCT/CA98/00274

Applicant: Dr. Isa Odidi and Dr. Amina Odidi

Title: **CONTROLLED RELEASE FORMULATION USING INTELLIGENT POLYMERS HAVING OPPOSING WETTABILITY CHARACTERISTICS OF HYDROPHOBICITY AND HYDROPHILICITY**

International Filing Date: 03/04/1998

Examiner: Ortega Plaza, M.D.

Date: May 11, 1999

DELIVERED VIA FACSIMILE (Confirmation by Courier)
(Fax No. 011-49-89-23 99-44 65)

REPLY

International Preliminary Examining Authority
European Patent Office
Erhardstrasse 27
D-80298 München
Germany

Dear Sirs:

This amendment is responsive to the Written Opinion dated February 11, 1999 in the above-identified International Application.

AMENDMENTS

Kindly replace pages 19 and 20 of the claims with new pages 19 and 20

which include amended claims 14 and 19.

REMARKS

The examiner asserts that claims 1-5, 6, 14, 16 and 20 lack novelty over D1 (US 5,000,962). Applicant respectfully submits that in D1 ethylcellulose was used as binder while in the present invention ethylcellulose is used as a release controlling polymer. In addition, the hydrophilic component of the present invention comprises two polymers while the example in D1 comprises a single polymer in each component. Thus, it is believed that claim 1 and the claims dependent therefrom distinguish over the D1 reference. Furthermore, in the D1 example 4% ethylcellulose was used while independent claim 14 specifies the use of ethylcellulose in an amount not less than 5% of the formulation. Thus, claim 14 and the claims dependent therefrom also distinguish from the D1 reference.

The examiner further asserts that claims 1, 2, 5, 10, 16-18, 28 and 29 lack novelty over D2 (EP-A-0226884). Applicant respectfully submits that the example referred to by the examiner addresses a completely different formulation with different release mechanisms and different release characteristics in vivo and in vitro. In the present claim 1, the hydrophilic component comprises two polymers and the hydrophobic component comprises one polymer while in D2 each component comprises a single polymer. Furthermore, mannitol is used in the cited example. There is no mention of the function that the mannitol is performing. In the present invention, mannitol is not used and lactose is used as a channelling agent. The channelling and wicking agents act in concert with the polymers to modulate the release of an active substance. In addition, the cited reference discloses a deposit core with a defined geometric form and a support platform applied to the deposit core. The support platform only partially coats the deposit core and it is not an anionic copolymer coating. In contrast, the present invention discloses an anionic copolymer coating which completely covers the tablet in one or more

concentric encasements. Unlike the cited example, the encasement coating of the present invention does not limit the swelling of tablets because it disintegrates completely via pH activation of surface groups. Therefore, claims 1, 2, 5, 10, 16-18, 28 and 29 distinguish over D2 (EP-A-0226884).

Applicant respectfully submits that cited reference D3 addresses a formulation and process that differs significantly from the present invention in that polymers are used alone in solution rather than as part of a hydrophobic or hydrophilic component.

Likewise, there is little similarity between the composition of example 3 of D4 that was cited by the examiner and the present invention. Claim 1 specifies that the hydrophilic component comprises two polymers and the hydrophobic component comprises one polymer. This feature also distinguishes over D5 that was cited by the examiner.

The examiner also asserts that the sustained release compositions of D8 fall within the scope of claim 1. The examiner concedes that the process as outlined in claim 23 differs from the method used to make the compositions of D8. Applicant submits that the process of the present patent will result in a completely different controlled release dosage form having different characteristics from that shown in example 7 of D8.

Finally, the examiner asserts that claim 1 lacks novelty vis-à-vis the contents of D10. Applicant respectfully submits that D10 does not disclose a hydrophilic component comprising two polymers and a hydrophobic component comprising one polymer.

In order to appreciate the novelty of the present invention over the cited references, it is necessary to consider the total formulation and not one excipient at a time since all of the agents in the formulation act in concert to modulate drug release. In view of the above, it is believed that the claims exhibit novelty over the cited references.

The examiner asserts that there is a lack of support in the disclosure for claim 27. Applicant respectfully submits that the effect of pH on the dissolution of the tablets is described on page 10 and one skilled in the art would readily be able to extrapolate the rates claimed in claim 27.

The examiner objected to claims 1, 14, and 19 as failing to include all of the technical features which characterize the invention. Applicant respectfully submits that the claims as they stand claim the essential features of the invention in a clear and complete manner sufficient to distinguish over the prior art. Inclusion within the claims of the specific limitations outlined by the examiner would unduly limit the scope of protection to which the applicant is entitled.

Claims 14 and 19 have been amended to include the phrase "by weight" as suggested by the examiner. Applicant does not wish to amend the claims at this time to delete the term "about" since this is considered an acceptable term in many Patent Offices and will be addressed in the national phase applications.

Respectfully submitted,

Patricia Rae
for Lola Bartoszewicz

PAR/ca
Encls

11. The composition of claim 10, wherein said channeling agent is anhydrous lactose.

12. The composition of claim 1, wherein said composition further comprises 5% to 30% compression enhancer.

13. The composition of claim 10, wherein said compression enhancer is microcrystalline cellulose.

14. A controlled release pharmaceutical composition comprising:

(a) from about 0.5% to about 70% by weight of a pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848;

(b) not less than about 5% by weight ethylcellulose;

(c) about 1:100 to 100:1 hydroxycellulose and hydroxypropyl methyl cellulose by weight;

(d) about 0.25% to 5% excipients; and

(e) about 0.5% to 15% surface active agents.

15. The composition of claim 14, wherein said composition additionally comprises

- about 10% to 70% channeling agents; and
- about 5% to 30% compression enhancers.

16. The composition as claimed in any one of claims 1 to 15, made in the form of a compressed tablet.

17. The tableted composition of claim 16, wherein said tableted composition has a anionic copolymer coating.

18. The tableted composition of claim 17, wherein said copolymer coating comprises methacrylic acid and methyl methacrylate, from about 0% to 25% plasticizer, from about 0% to 25% pigment, from about 0% to 30% glidant and from about 0% to 30% lubricant.

19. A controlled release composition, the composition comprising a therapeutically effective amount of a pharmaceutically active ingredient having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848; two groups of intelligent polymers having opposing wettability characteristics, one group demonstrating a stronger tendency towards hydrophobicity and present in an amount not less than 5% wt/wt and the other group having a

stronger tendency towards hydrophilicity and present in the ratio of about 1:100 and 100:1 by weight, the polymers being ethylcellulose (EC) as a more strongly hydrophobic and hydroxyethylcellulose (HEC) and hydroxypropyl methylcellulose (HPMC) as more strongly hydrophilic, about 0.25% to 5% silicon dioxide; and about 0.5% to 15% sodium lauryl sulfate.

20. The composition of claim 19, wherein said composition additionally comprises about 10% to 70% anhydrous lactose and about 5% to 30% microcrystalline cellulose.

21. The composition of claim 18 or 20, wherein said composition is provided as a tablet and has a coating composition comprising anionic copolymers sufficient to obtain about 0.5 to 15 mg per cm^2 of tablet.

22. The composition of claim 21, wherein said coating composition additionally comprises from about 0 to 25% plasticizer, about 0 to 25% pigment, about 0 to 30% and about 0 to 30% lubricant.

23. A process for the manufacture of a sustained release composition of pharmaceutically active substance, said process comprising:

(a) admixing a pharmaceutically active substance having a water contact angle (θ) such that cos θ is between +0.9848 and -0.9848:

(b) blending the pharmaceutically active ingredient with about 5 to 25% hydroxypropyl methylcellulose, about 1 to 25% hydroxyethylcellulose, about 0.25% to 5% suitable pharmaceutical excipients, about 0.5% to 15% suitable surface active agents, and about 10% to 70% chanelling agents in a high shear mixer until a homogeneous mixture is obtained;

(c) granulating the homogeneous blend with isopropyl alcohol (99%) in a planetary or high shear mixer;

(d) drying the wet granules to a loss on drying of about <3% and organic volatile impurities of isopropyl alcohol about <15000 ppm;

(e) milling the dry granules to about <1500 microns;

(f) adding and blending about 5% to 70% of ethylcellulose having 30-60% ethoxyl content and a vicosity of 60- 100 cps to the dry milled granules until a homogeneous blend is obtained;